

PROTAMINE SULFATE- protamine sulfate injection, solution
HF Acquisition Co LLC, DBA HealthFirst

PROTAMINE SULFATE INJECTION, USP 50mg/5mL (10mg/mL) 5mL VIAL

BOXED WARNING

WARNING

Protamine sulfate can cause severe hypotension, cardiovascular collapse, noncardiogenic pulmonary edema, catastrophic pulmonary vasoconstriction, and pulmonary hypertension. Risk factors include high dose or overdose, rapid administration (see WARNINGS and DOSAGE AND ADMINISTRATION), repeated doses, previous administration of protamine, and current or previous use of protamine-containing drugs (NPH insulin, protamine zinc insulin, and certain beta-blockers). Allergy to fish, previous vasectomy, and severe left ventricular dysfunction and abnormal preoperative pulmonary hemodynamics also may be risk factors. In patients with any of these risk factors, the risk to benefit of administration of protamine sulfate should be carefully considered. Vasopressors and resuscitation equipment should be immediately available in case of a severe reaction to protamine. Protamine sulfate should not be given when bleeding occurs without prior heparin use.

SPL UNCLASSIFIED

For Intravenous Use

DESCRIPTION

Protamines are simple proteins of low molecular weight that are rich in arginine and strongly basic. They occur in the sperm of salmon and certain other species of fish.

Protamine sulfate occurs as fine white or off-white amorphous or crystalline powder. It is sparingly soluble in water. The pH is between 6.0 and 7.0. The cationic hydrogenated protamine at a pH of 6.8 to 7.1 reacts with anionic heparin at a pH of 5.0 to 7.5 to form an inactive complex.

Protamine Sulfate Injection, USP is a sterile, isotonic solution of protamine sulfate. It acts as a heparin antagonist. It is also a weak anticoagulant.

Each mL contains: Protamine sulfate 10 mg; sodium chloride 9 mg; Water for Injection q.s. Sulfuric acid and/or dibasic sodium phosphate (heptahydrate) may have been added for pH adjustment.

The preparation is preservative free.

Protamine sulfate is administered intravenously.

CLINICAL PHARMACOLOGY

When administered alone, protamine has an anticoagulant effect. However, when it is given in the presence of heparin (which is strongly acidic), a stable salt is formed and the anticoagulant activity of both drugs is lost.

Protamine sulfate has a rapid onset of action. Neutralization of heparin occurs within five minutes after intravenous administration of an appropriate dose of protamine sulfate. Although the metabolic fate of the heparin-protamine complex has not been elucidated, it has been postulated that protamine sulfate in the heparin-protamine complex may be partially metabolized or may be attacked by fibrinolysin, thus freeing heparin.

INDICATIONS & USAGE

Protamine Sulfate Injection, USP is indicated in the treatment of heparin overdosage.

CONTRAINDICATIONS

Protamine sulfate is contraindicated in patients who have shown previous intolerance to the drug.

WARNINGS

Hyperheparinemia or bleeding has been reported in experimental animals and in some patients 30 minutes to 18 hours after cardiac surgery (under cardiopulmonary bypass) in spite of complete neutralization of heparin by adequate doses of protamine sulfate at the end of the operation. It is important to keep the patient under close observation after cardiac surgery. Additional doses of protamine sulfate should be administered if indicated by coagulation studies, such as the heparin titration test with protamine and the determination of plasma thrombin time.

Too-rapid administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions (see DOSAGE & ADMINISTRATION and WARNINGS). Facilities to treat shock should be available.

PRECAUTIONS

General

Because of the anticoagulant effect of protamine, it is unwise to give more than 50 mg over a short period unless a larger dose is clearly needed.

Patients with a history of allergy to fish may develop hypersensitivity reactions to protamine, although to date no relationship has been established between allergic reactions to protamine and fish allergy.

Previous exposure to protamine can induce a humoral immune response and predispose susceptible individuals to the development of untoward reactions from the subsequent use of this drug. Patients exposed to protamine through the use of protamine-containing insulin or during heparin neutralization may experience life-threatening reactions and fatal anaphylaxis upon receiving large doses of protamine intravenously. Severe reactions to intravenous protamine can occur in the absence of local or systemic allergic reactions to subcutaneous injection of protamine-containing insulin. Reports of the presence of antiprotamine antibodies in the sera of infertile or vasectomized men suggest that some of these individuals may react to the use of protamine sulfate.

Fatal anaphylaxis has been reported in one patient with no prior history of allergies.

Drug Interactions

Protamine sulfate has been shown to be incompatible with certain antibiotics, including several of the cephalosporins and penicillins (see DOSAGE & ADMINISTRATION).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been performed to determine potential for carcinogenicity, mutagenicity or impairment of fertility.

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with protamine sulfate. It is also not known whether protamine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Protamine sulfate should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when protamine sulfate is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The intravenous administration of protamine sulfate may cause a sudden fall in blood pressure and bradycardia. Other reactions include transitory flushing and feeling of warmth, dyspnea, nausea, vomiting and lassitude. Back pain has been reported in conscious patients undergoing such procedures as cardiac catheterization.

Severe adverse reactions have been reported including: (1) Anaphylaxis that resulted in severe respiratory distress, circulation collapse and capillary leak (see PRECAUTIONS). Fatal anaphylaxis has been reported in one patient with no prior history of allergies; (2) Anaphylactoid reactions with circulatory collapse, capillary leak, and noncardiogenic pulmonary edema; acute pulmonary hypertension.

Complement activation by the heparin-protamine complexes, release of lysosomal enzymes from neutrophils, and prostaglandin and thromboxane generation have been associated with the development of anaphylactoid reactions.

Severe and potentially irreversible circulatory collapse associated with myocardial failure and reduced cardiac output can also occur. The mechanism(s) of this reaction and the role played by concurrent factors are unclear.

High-protein, noncardiogenic pulmonary edema associated with the use of protamine has been reported in patients on cardiopulmonary bypass who are undergoing cardiovascular surgery. The etiologic role of protamine in the pathogenesis of this condition is uncertain, and multiple factors have been present in most cases. The condition has been reported in association with administration of certain blood products, other drugs, cardiopulmonary bypass alone, and other etiologic factors. It is difficult to treat, and it can be life-threatening. Because fatal anaphylactic and anaphylactoid reactions have been reported after the administration of protamine sulfate, the drug should be given only when resuscitation techniques and treatment of anaphylactic and anaphylactoid shock are readily available.

OVERDOSAGE

Signs and Symptoms

Overdose of protamine sulfate may cause bleeding. Protamine has a weak anticoagulant effect due to an interaction with platelets and with many proteins including fibrinogen. This effect should be distinguished from the rebound anticoagulation that may occur 30 minutes to 18 hours following the reversal of heparin with protamine.

Rapid administration of protamine is more likely to result in bradycardia, dyspnea, a sensation of warmth, flushing, and severe hypotension. Hypertension has also occurred.

The median lethal dose of protamine sulfate is 50 mg/kg in mice. Serum concentrations of protamine sulfate are not clinically useful. Information is not available on the amount of drug in a single dose that is associated with overdosage or is likely to be life-threatening.

Treatment

To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the Physicians' Desk Reference (PDR). In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs and unusual drug kinetics in your patient.

Replace blood loss with blood transfusions or fresh frozen plasma.

If the patient is hypotensive, consider fluids, epinephrine, dobutamine or dopamine.

DOSAGE & ADMINISTRATION

Each mg of protamine sulfate, calculated on the dried basis, neutralizes not less than 100 USP Heparin Units.

Protamine sulfate injection should be given by very slow intravenous injection over a 10-minute period in doses not to exceed 50 mg (see WARNINGS).

Protamine sulfate is intended for injection without further dilution; however, if further dilution is desired, D5-W or normal saline may be used. Diluted solutions should not be stored since they contain no preservative.

Protamine sulfate should not be mixed with other drugs without knowledge of their compatibility, because protamine sulfate has been shown to be incompatible with certain antibiotics, including several of the cephalosporins and penicillins.

Because heparin disappears rapidly from the circulation, the dose of protamine sulfate required also decreases rapidly with the time elapsed following intravenous injection of heparin. For example, if the protamine sulfate is administered 30 minutes after the heparin, one-half the usual dose may be sufficient.

The dosage of protamine sulfate should be guided by blood coagulation studies (see WARNINGS).

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

PROTAMINE SULFATE INJECTION, USP is supplied in the following dosage forms.

NDC 51662-1414-1

PROTAMINE SULFATE INJECTION, USP 50mg/5mL (10mg/mL) 5mL VIAL

HF Acquisition Co LLC, DBA HealthFirst
Mukilteo, WA 98275

Also supplied in the following manufacture supplied dosage forms

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not permit to freeze.

CAUTION: The total dose of protamine sulfate contained in product No. 22925 and 22930 (250 mg in 25 mL) is 5 times greater than in product No. 22905 (50 mg in 5 mL).

The large size 25 mL vials are designed for antiheparin treatment only when large doses of heparin have been given during surgery and are to be neutralized by large doses of protamine sulfate after surgical procedures.

Product No.	NDC No.	
22905	63323-229-05	Protamine Sulfate Injection, USP, 50 mg per 5 mL (10 mg per mL) in a 5 mL single dose flip-top vial, in packages of 25.
22925	63323-229-25	Protamine Sulfate Injection, USP, 250 mg per 25 mL (10 mg per mL) in a 25 mL single dose flip-top vial, in packages of 10.
22930	63323-229-30	Protamine Sulfate Injection, USP, 250 mg per 25 mL (10 mg per mL) in a 25 mL single dose flip-top vial, packaged individually.

SPL UNCLASSIFIED



www.fresenius-kabi.us

45848G

Revised: December 2016

PRINCIPAL DISPLAY PANEL - VIAL LABEL



NDP 63329-229-05 4

Protamine Sulfate

Injection, USP

50 mg per 5 mL

(10 mg per mL)

**For Intravenous
Use Only**

Rx only
5 mL Single Dose Vial

Sterile, Nonpyrogenic
Preservative Free.

Discard unused portion.

Each mL contains: Protamine sulfate
10 mg, sodium chloride 9 mg. Vialster for

Protamine
sulfate
USP
5 mL

venous

Rx only
Single Dose Vial

Sterile, Nonpyrogenic

Preservative Free.

Discard unused portion.

Each mL contains: Protamine sulfate
10 mg; sodium chloride 9 mg; Water for
Injection q.s. Sulfuric acid and/or dibasic
sodium phosphate (heptahydrate) may
have been added for pH adjustment.

Usual Dosage: See insert.

Each mg of protamine sulfate, calcu-
lated on the dried basis, neutralizes not
less than 100 USP Heparin Units.

Store at 20° to 25°C (68° to 77°F) (see
USP Controlled Room Temperature).

Discard unused portion.
Each mL contains: Protamine sulfate
10 mg; sodium chloride 9 mg; Water for
Injection q.s. Sulfuric acid and/or dibasic
sodium phosphate (heptahydrate) may
have been added for pH adjustment.

Usual Dosage: See insert.

Each mg of protamine sulfate, calcu-
lated on the dried basis, neutralizes not
less than 100 USP Heparin Units.

**Store at 20° to 25°C (68° to 77°F) [see
USP Controlled Room Temperature].**

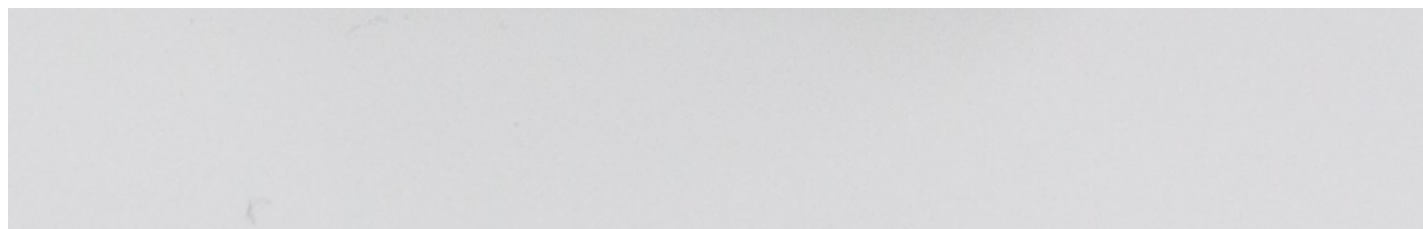
Do not permit to freeze.

Fresenius Kabi

Lake Zurich, IL 60047

401879G

LOT 1515



Fresenius Kabi
Lake Zurich, IL 60047

401879G

LOT/EXP

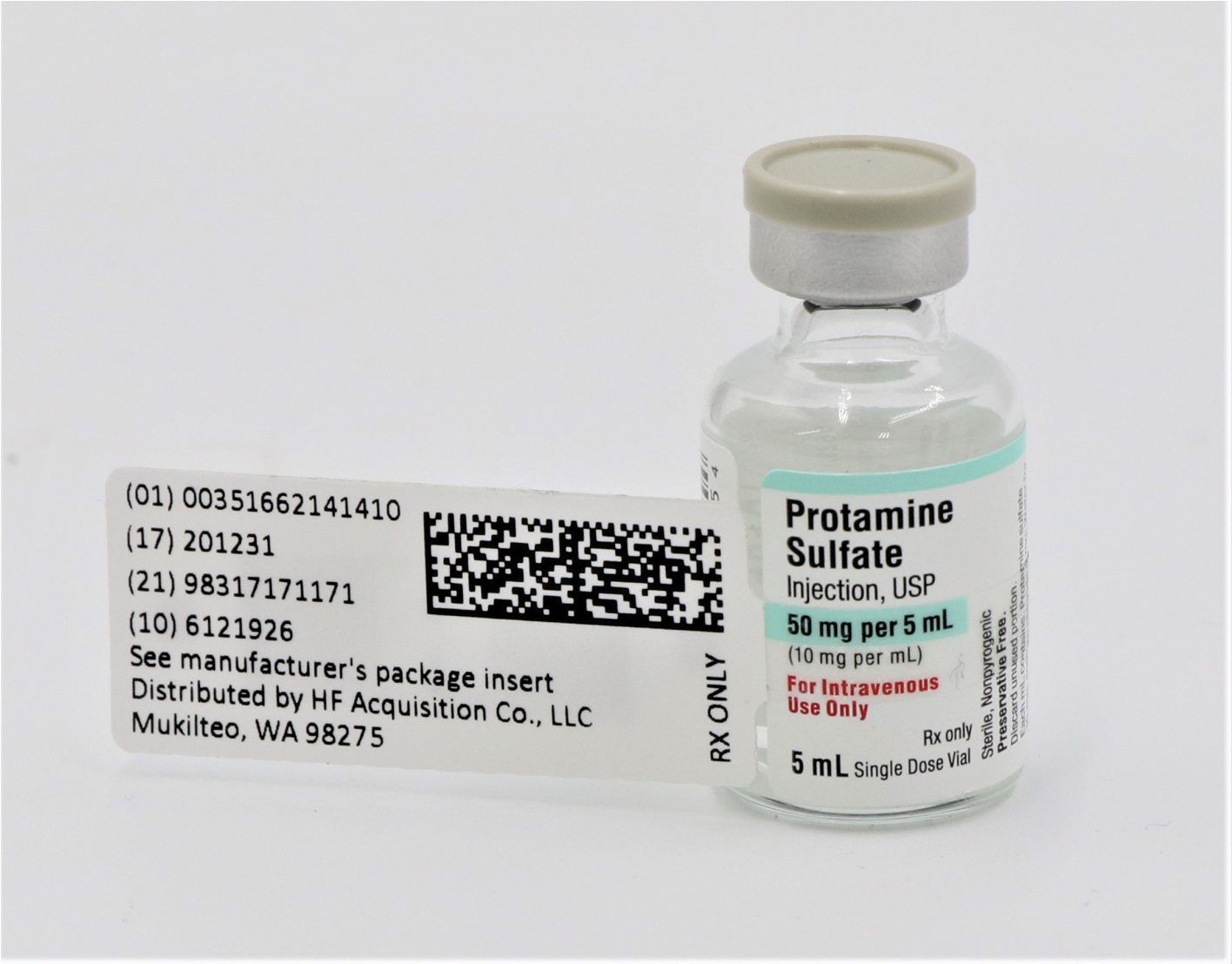
LOT 6121926

EXP 12/20



3 NDC 63323-229-05 4

PRINCIPAL DISPLAY PANEL - SERIALIZED LABELING



PROTAMINE SULFATE

protamine sulfate injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:51662-1414(NDC:63323-229)
Route of Administration	INTRAVENOUS		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
PROTAMINE SULFATE (UNII: 0DE9724IHC) (PROTAMINE - UNII:72G3UY6T4N)		PROTAMINE SULFATE	10 mg in 1 mL
Inactive Ingredients			
Ingredient Name			Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)			9 mg in 1 mL

SODIUM PHOSPHATE, DIBASIC (UNII: GR686LBA74)				
SULFURIC ACID (UNII: O40UQP6WCF)				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:51662-1414-1	5 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product	10/13/2019	
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA		ANDA089454	10/13/2019	

Labeler - HF Acquisition Co LLC, DBA HealthFirst (045657305)

Registrant - HF Acquisition Co LLC, DBA HealthFirst (045657305)

Establishment			
Name	Address	ID/FEI	Business Operations
HF Acquisition Co LLC, DBA HealthFirst		045657305	relabel(51662-1414)